New Definition for the Partial Remission Period in Children and Adolescents With Type 1 Diabetes

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OBJECTIVE — To find a simple definition of partial remission in type 1 diabetes that reflects both residual β-cell function and efficacy of insulin treatment.

RESEARCH DESIGN AND METHODS — A total of 275 patients aged <16 years were followed from onset of type 1 diabetes. After 1, 6, and 12 months, stimulated C-peptide during a challenge was used as a measure of residual β-cell function.

RESULTS — By multiple regression analysis, a negative association between stimulated C-peptide and A1C (regression coefficient −0.21, $P < 0.001$) and insulin dose (−0.94, $P < 0.001$) was shown. These results suggested the definition of an insulin dose–adjusted A1C (IDAA1C) as A1C (percent) + [4 × insulin dose (units per kilogram per 24 h)]. A calculated IDAA1C ≤9 corresponding to a predicted stimulated C-peptide >300 pmol/l was used to define partial remission. The IDAA1C ≤9 had a significantly higher agreement ($P < 0.001$) with residual β-cell function than use of a definition of A1C ≤7.5%. Between 6 and 12 months after diagnosis, for IDAA1C ≤9 only 1 patient entered partial remission and 61 patients ended partial remission, for A1C ≤7.5% 15 patients entered partial remission and 53 ended, for a definition of insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1} 5 patients entered partial remission and 66 ended, and for stimulated C-peptide (>300 pmol/l) 9 patients entered partial remission and 49 ended. IDAA1C at 6 months has good predictive power for stimulated C-peptide concentrations after both 6 and 12 months.

CONCLUSIONS — A new definition of partial remission is proposed, including both glycemic control and insulin dose. It reflects residual β-cell function and has better stability compared with the conventional definitions.

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Clinically, newly diagnosed type 1 diabetes is characterized by a transient partial remission period ("honeymoon"), starting shortly after insulin treatment is initiated and during which the patient's need for exogenous insulin treatment declines and in some cases even totally disappears, and metabolic control is near optimal. The pathogenesis of this phenomenon has been the subject of discussion (1) but is likely to be a combination of two factors: partial β-cell recovery with improved insulin secretion (2) and improvement of peripheral insulin sensitivity (3).

The definition of the partial remission period has varied greatly in the past. Most authors define partial remission as an insulin requirement of ≤0.5 units · kg^{-1} · 24 h^{-1} (4–6). However, it is not useful to define a disease state by the treatment applied, and the insulin dose is influenced by a large number of other factors. At best, this definition is reasonable when the treatment policy is uniform, which is rarely the case, even within single centers and even less so in a multicenter international study. As an extreme consequence of this definition, a diabetic patient is considered to be in partial remission when treated with a relatively low dose of insulin. To correct for this problem, others have used the definition as an A1C close to or within the normal range (7). This definition is also influenced by the treatment, as increasing the insulin dose lowers the A1C level. Furthermore, there is an initial time delay from the time of diagnosis of 4–6 weeks before a new steady-state A1C can be achieved (8). Somewhat more relevant is to combine the two definitions, that is, an insulin requirement of ≤0.5 units · kg^{-1} · 24 h^{-1} in combination with A1C ≤7.5% (9,10). Others have used an even lower limit for insulin requirement such as 0.3 units · kg^{-1} · 24 h^{-1} (11). Combining the two parameters is better than using either one alone, but having separate limits on each variable still causes a problem with the definition because a treatment change easily influences the classification of a patient.

As another possibility, Komulainen et al. (12) used a basal C-peptide level of 100 pmol/l as an index for residual β-cell function. Although fasting C-peptide alone may be relatively easy to obtain in research centers and correlates with stimulated C-peptide, it is insufficient for detecting dynamic changes in residual β-cell function. Serial measurements of

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stimulated C-peptide that directly reflect residual β-cell function have therefore become the standard for evaluation of endogenous insulin secretion (13), but no definitions of partial remission based on stimulated C-peptide have been proposed. Besides, determination of stimulated C-peptide is a laborious, expensive, and time-consuming process and is unpleasant for the child (the patient has no breakfast and then undergoes a 90-min study and delays the morning insulin dose). Therefore, it would be useful to have an easy clinical measure for partial remission somewhat similar to the homeostasis model assessment for insulin resistance and β-cell function (14). The objective of the current longitudinal investigation was therefore to evaluate the relation between A1C and insulin dose, which are both routinely measured in clinical practice, to create a surrogate measure of stimulated C-peptide and near-normal glycemia. Furthermore, we aimed to examine the validity and reliability of this measure.

RESEARCH DESIGN AND METHODS

The study was a multicenter longitudinal investigation in 18 pediatric departments representing 15 countries in Europe and Japan. A total of 275 children and adolescents aged <16 years with newly diagnosed type 1 diabetes presenting to the pediatric departments between August 1999 and December 2000 were included in the study. Exclusion criteria were suspicion of non–type 1 diabetes (e.g., maturity-onset diabetes of the young or secondary diabetes) and initial treatment outside of the centers for >5 days. Diabetes was diagnosed according to the World Health Organization criteria. Of the patients, 84% were white, mean ± SD age at clinical diagnosis was 9.1 ± 3.7 years, and BMI was 16.5 ± 3.2 kg/m^2. Insulin regimens were recorded 1, 3, 6, 9, and 12 months after diagnosis. After 12 months, 52.9% of the children were taking insulin twice daily, 25% three times daily, and 18.5% four or more times daily. Only a few children (3.3%) received one insulin injection daily. A premixed form of insulin was used in 72.3% of the children taking insulin twice daily. Only three children used an insulin infusion pump, and 13% were treated with a rapid-acting insulin analog. The mean daily insulin dose was 0.7 ± 0.3 units/kg. For the new measure to cover different insulin policies, local centers were not instructed to follow a specific insulin treatment program.

The study was performed according to the criteria of the Helsinki II Declaration (15) and was approved by the local ethics committee in each center. All of the patients and their parents or guardians gave informed consent.

A1C

Samples for A1C analysis were collected at onset and after 1, 3, 6, 9, and 12 months at each department using the Bio-Rad A1C sample preparation kit (Bio-Rad Laboratories, Munich, Germany) and mailed to the Steno Diabetes Centre (Copenhagen, Denmark) as described before (16). The A1C analysis was performed by automatic high-pressure liquid chromatography with the same calibrator lots as used in the Diabetes Control and Complications Trial (DCCT) to facilitate comparisons with this study. Normal range for A1C for the method at Steno Diabetes Center was 4.4–6.3% (~0.3% higher than the DCCT method).

C-peptide

After 1, 6, and 12 months of diabetes, a standard liquid meal was used to stimulate endogenous C-peptide release (17). Serum samples were labeled and frozen at –20°C until shipment on dry ice to the Steno Diabetes Centre for the determination of C-peptide within 6 months. Samples were thawed only once for RIA determination. Serum C-peptide was analyzed by a fluoroimmunometric assay (AutoDELFIA C-peptide; PerkinElmer Life and Analytical Sciences, Turku, Finland). The analytical sensitivity was better than 5 pmol/l, the intra-assay coefficient of variation was <6% at 20 pmol/l, and recovery of standard, added to plasma before extraction, was ~100% when corrected for losses inherent in the plasma extraction procedure.

Statistics

A1C and insulin dose cannot be considered separately because the measured A1C will be influenced by the insulin dose as well as by the residual β-cell function. The idea was to combine the two to suggest a new measure of insulin dose–adjusted A1C (IDAA1C) that was relatively less influenced by treatment policy. A unified suggestion, in which both A1C and insulin dose were included, was investigated by multiple regression analysis with the logarithm of stimulated C-peptide as the dependent variable and sex, age, A1C, and daily insulin dose (units per kilogram body weight) as independent variables 6 and 12 months after diagnosis.

In the DCCT, a limit of 300 pmol/l was defined as the level for "the C-peptide responders" (200–500 pmol/l). We aimed to define partial remission in alignment with the DCCT (17) as an IDAA1C predicting a C-peptide response of >300 pmol/l.

To investigate the influence of age on the proportion of patients in remission, the insulin requirement and A1C values during the follow-up were analyzed with the patients divided into age-groups (0–4.9, 5.0–9.9, and 10.0–16 years). Age-group comparisons versus IDAA1C ≤9 were done by a χ^2 test for the count of patients.

To compare the various definitions, the proportion of children in partial remission as defined by each definition was evaluated at 3, 6, 9, and 12 months. The insulin dose used to calculate the rate of partial remission was the value before the visit because A1C reflects the blood glucose level over the previous 4- to 6-week period (8).

A statistical comparison was performed to evaluate the concurrent agreement of A1C, IDAA1C, and stimulated C-peptide. Agreement between the definitions was examined by plotting 12-month values for stimulated C-peptide against both A1C and IDAA1C and with summary statistics for the percentage of agreement with stimulated C-peptide. This latter comparison was supplemented with a formal χ^2 test of which parameters of A1C or IDAA1C are most closely related to C-peptide, by constructing a 2 × 2 × 2 table of classifications based on A1C, IDAA1C, and stimulated C-peptide. In this table, we tested whether A1C ≤7.5 or >7.5% had an influence on stimulated C-peptide when the IDAA1C classification was included. For each IDAA1C group (≤9, respectively, >9) this consisted of a test of independence of A1C group and stimulated C-peptide group. A similar test was done with A1C and IDAA1C with reversed roles. The two test statistics were then added to obtain a joint conclusion regarding which of the two measures gave the best agreement with the C-peptide definition.

To confirm the validity of IDAA1C at 12 months, the relationship of stimulated C-peptide and IDAA1C at 6 and 12 months was investigated by linear regres-

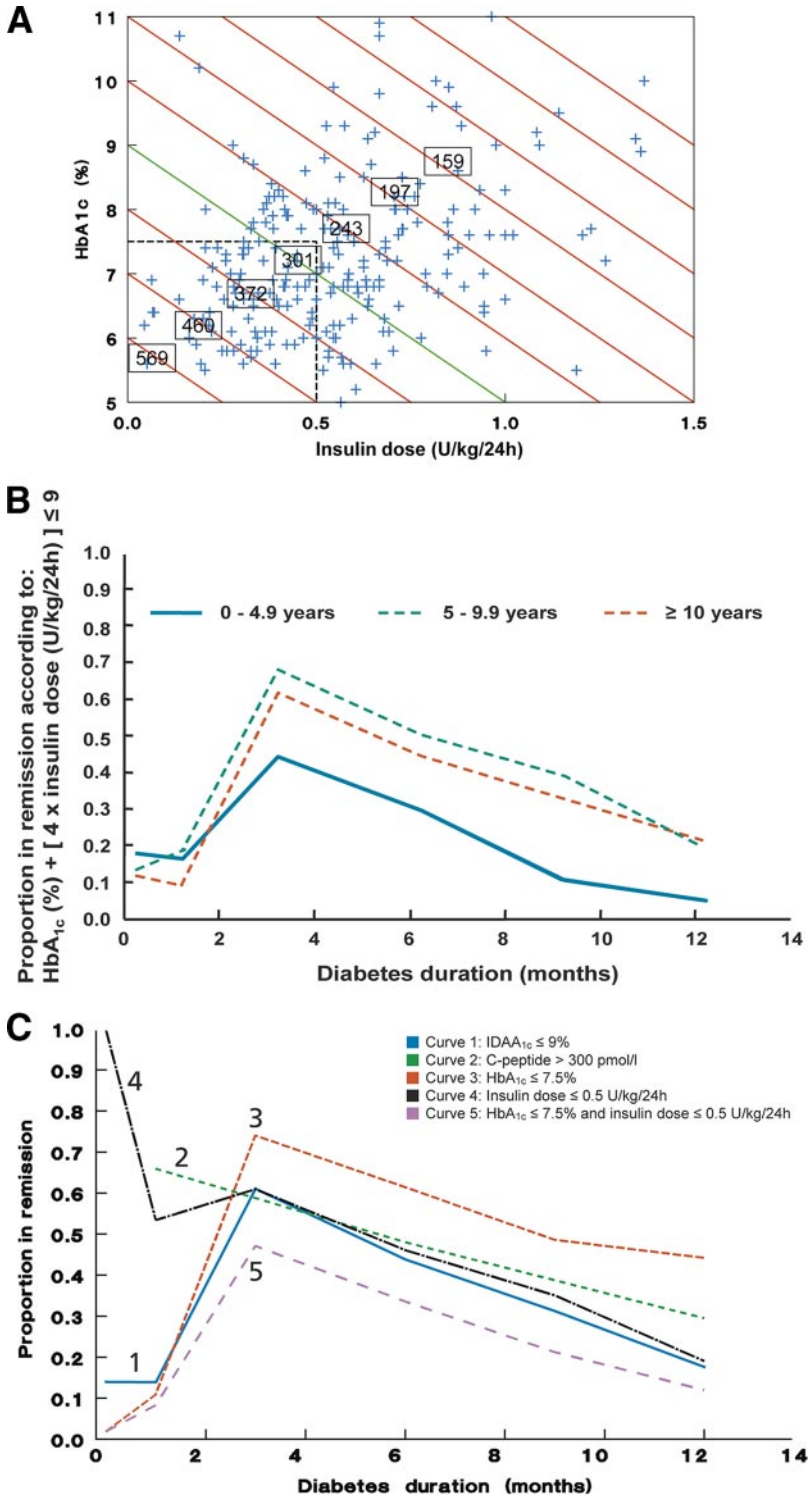
sion according to duration and IDAA1C but not sex and age. To examine the predictive validity of IDAA1C, A1C and insulin dose data from 1 and 6 months were used in a multiple regression model (including covariates age and sex) to predict C-peptide responses (logarithmic scale) at 6 and 12 months, respectively. To examine the agreement between the two definitions (IDAA1C ≤9 and stimulated C-peptide >300 pmol/l), a χ^2 test was performed in the 2 × 2 table of classifications based on IDAA1C and stimulated C-peptide. The stability of the IDAA1C-defined partial remission was investigated by comparing the number of subjects transitioning in and out of partial remission defined by IDAA1C and by other definitions of partial remission over the period of 6–12 months.

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). $P < 0.05$ was considered significant.

RESULTS

Partial remission defined by IDAA1C

The multivariate analysis showed a negative correlation between stimulated C-peptide, A1C, and insulin dose, with a significant effect of age (estimate 0.09/year, $P < 0001$) but not sex (estimate comparing female with male patients −0.01, $P = 0.91$) at 6 months after diagnosis. It would be natural to include an age effect in the formula, if the aim of the study had purely been to predict the stimulated C-peptide level. However, because the purpose was to suggest a new measure for remission, it was anticipated that the suggested formula for IDAA1C could be useful on its own and therefore age was not included. From the regression coefficients at 6 months (A1C −0.21 and insulin dosage −0.94), it was seen that there was a factor of ~4.4 between the coefficients for these parameters. The R^2 value was 0.30. Results at 6 and 12 months were similar. This finding inspired the suggestion of a combined expression of insulin dose and A1C, formulated as a specific definition of the IDAA1C = A1C (percent) + 4 × [insulin dose (units per kilogram per 24 h)]. The factor of 4.4 was substituted by 4 to obtain simple numbers. Based on the slope of the regression line between stimulated C-peptide, A1C, and insulin dose, a predicted C-peptide value can be calculated from any given set of corresponding A1C and insulin dose.



The distribution of patients according to individual A1C and insulin dosages at 6 months' duration are shown in Fig. 1*A*, in which each diagonal red line corresponds to one IDDA1C value. According to this model an IDAA1C threshold ≤9 corresponds to a predicted level of >300 pmol/l for the corresponding stimulated C-peptide. This expression can be used as a qualitative measure of partial remission, and in alignment with the DCCT "C-peptide responders" (200–500 pmol/l), we have chosen IDAA1C ≤9 to define partial remission. Other threshold values

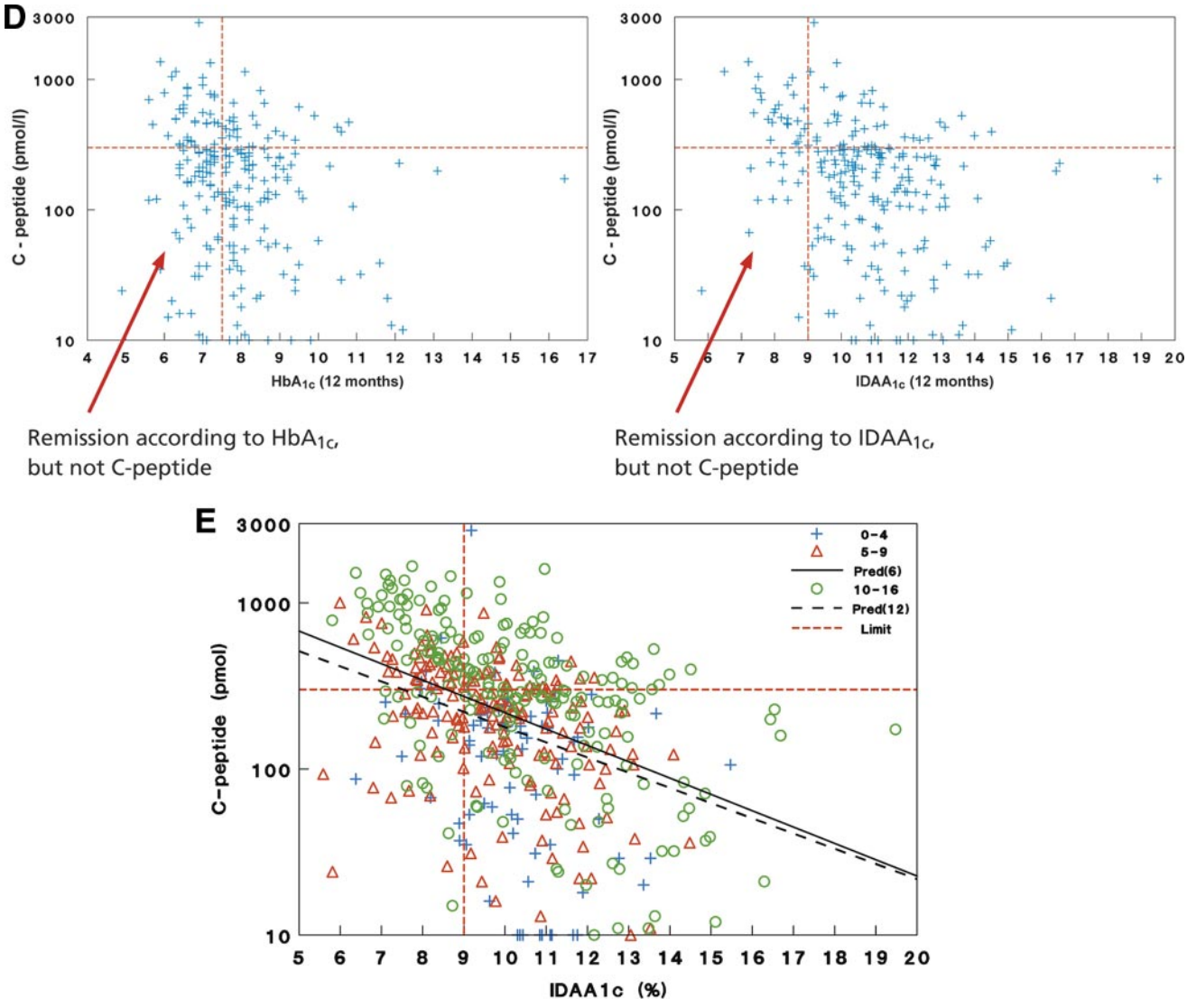


Figure 1—A: *The thresholds for partial remission based on IDAA1C ≤9* (solid green line) *and A1C ≤7.5% and insulin doses ≤0.5 units · kg^{-1} · 24 h^{-1}* (rectangular dashed box). *Each diagonal red line corresponds to one IDAA1C value. The numbers in boxes are the predicted values for stimulated C-peptide concentrations for a 10-year-old boy at the relevant IDAA1C value and, as illustrated, other threshold values for IDAA1C correspond to different predicted C-peptide values. The + signs give the distribution of 257 patients with type 1 diabetes after 6 months' duration.* B: *Age at onset influences the rate of partial remission as assessed by IDAA1C in children with type 1 diabetes. The proportion of partial remission is lowest in the youngest age-group (0–4.9 years). Because of lower insulin sensitivity, the proportions of partial remission in the old age-group (≥10 years) and the school-age children (5–9.9 years) seem to be similar despite higher residual β-cell function.* C: *The proportion of children in partial remission according to the different definitions. From 3 to 12 months, the curves for IDAA1C (curve 1), C-peptide (curve 2), and insulin dose (curve 4) show close agreement. Using the new definition, partial remission occurred in 61% at 3 months, in 44% at 6 months, and in 18% after 12 months.* D: *Agreement between definitions of those in partial remission, A1C ≤7.5%* (left panel, dashed vertical line), *IDAA1C ≤9* (right panel, dashed vertical line), *and stimulated C-peptide >300 pmol/l* (dashed horizontal line) *at 12 months. The arrows point to the areas showing that A1C ≤7.5% disagrees significantly more than IDAA1C ≤9 with C-peptide >300 pmol/l, probably because the children receive more exogenous insulin, which is accounted for in the insulin dose–adjusted model.* E: *The relationship of IDAA1C ≤9* (dashed vertical line) *and stimulated C-peptide >300 pmol/l* (dashed horizontal line) *at 6 and 12 months. Individual observations are shown by age-groups. The regression lines for 6 (——) and 12 (– – –) months show the linear correlation of IDAA1C and C-peptide over a continuum of stimulated C-peptide values.*

for IDAA1C could have been chosen, corresponding to different predicted C-peptide values. Compared with the partial remission definition, insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1} and A1C ≤7.5% (Fig. 1*A*, rectangular dashed box), our definition has been extended with the triangular area above and to the right side of the rectangular dashed box. As an indicator of more aggressive insulin therapy at some of the centers, there are more patients placed in the triangle to the right of the dashed line that marks an insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1} than in the upper triangle above the dashed line, marking an A1C ≤7.5%.

Partial remission by IDAA1C and influence of age

Figure 1*B* shows that age at onset influences the rate of partial remission in children with type 1 diabetes. Significantly ($P < 0.05$) fewer patients in the young age-group (0–5 years) were in partial remission (3–9 months, $P < 0.01$) com-

pared with those in the older age-groups. After 12 months, only 5% of the very young children are in partial remission compared with 20% of those in the older age-groups.

Table 1—*Partial remission transitions from 6 to 12 months*

PR definition	In PR at 6 months/proportion in PR at 12 months	Not in PR at 6 months/proportion in PR at 12 months
IDAA1C ≤9	37/98 (38)	1/122 (1)
A1C ≤7.5%	87/140 (62)	15/85 (18)
Insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1}	46/112 (41)	5/123 (4)
C-peptide >300 pmol/l	58/107 (54)	9/119 (8)

Data are *n* (%). PR, partial remission.

Comparison of partial remission by IDAA1C with existing definitions

The proportion of children in partial remission according to various definitions is shown in Fig. 1*C* as a function of diabetes duration. Because the A1C level at 1 month still reflects glycemia before diagnosis, the comparison between the different definitions of partial remission was performed at 3 months. From 3 to 12 months, the curves for IDAA1C (curve 1), C-peptide (curve 2), and insulin dose (curve 4) show close agreement. The definition of partial remission including insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1} and A1C ≤7.5% (curve 5) suggests that fewer patients are in partial remission, and A1C ≤7.5% without insulin dose adjustment (curve 3) suggests that more patients are in partial remission after 3 months. Using the new definition, partial remission occurred in 61% at 3 months, in 44% at 6 months, and in 18% after 12 months.

Agreements between A1C, IDAA1C, and stimulated C-peptide

The agreement between definitions of those in partial remission by A1C ≤7.5% and by IDAA1C ≤9 compared with residual β-cell function with C-peptide >300 pmol/l is shown in Fig. 1*D*. The definitions agree in the upper left quadrant and the lower right quadrant of the diagrams. However, for A1C (Fig. 1*D*, *left panel*) there are significantly more patients in the lower left quadrant of the diagram with an A1C ≤7.5% but with a residual β-cell function ≤300 pmol/l than for IDAA1C (Fig. 1*D*, *right panel*), probably because the children with low residual β-cell function who are receiving aggressive insulin treatment are more accurately accounted for in the dose-adjusted model (see formal χ^2 test in the next paragraph). A formal test of the strength of the relationship between each definition and stimulated C-peptide at 6 months was performed in a model, in which the classifications of partial remission according to both A1C and IDAA1C were allowed an effect on the C-peptide definition of partial remission (>300 pmol/l).

In the joint test, A1C was not significant ($\chi^2 = 2.40$, 2 df, $P = 0.30$), whereas IDAA1C was clearly significant ($\chi^2 = 11.07$, 2 df, $P = 0.004$).Thus, IDAA1C gives the best agreement with the C-peptide definition. The same conclusion was reached after 12 months.

Correlation between IDAA1C and actual C-peptide response at 6 and 12 months

The relationship of IDAA1C and stimulated C-peptide at 6 and 12 months is shown in Fig. 1*E*. The regression curves suggest a tendency toward higher stimulated C-peptide values at 6 months compared with 12 months, also when related to IDAA1C. Overall, the predictive value of IDAA1C in combination with sex and age was good ($R^2 = 0.30$ at 6 months and $R^2 = 0.31$ at 12 months).

IDAA1C at 1 and 6 months as predictor of future values of C-peptide response

In predicting C-peptide after 6 months based on 1 month of data and after 12 months based on 6 months of data, using sex, age, A1C, and insulin dose, we found that there was a significant dependence on both A1C and insulin dose, but the effect of these could be adequately summarized by the IDAA1C. The coefficients in the final model for predicting (log) C-peptide after 12 months was sex (estimate for female patients −0.11, $P = 0.40$), age (estimate 0.13, $P < 0.001$), and IDAA1C after 6 months (estimate −0.32, $P < 0.001$).

Stability of IDAA1C-defined partial remission in the prepubertal compared with older age-groups

Only a few of the very young children (0–4 years) are in partial remission using any of the two definitions (stimulated C-peptide >300 pmol/l or IDAA1C ≤9). The older children (10–16 years) have relatively higher C-peptide values; thus, the patients, who are in partial remission according to C-peptide but not IDAA1C, are mostly older and presumably with more insulin resistance due to puberty, whereas those who are not in partial remission according to C-peptide but are in partial remission according to IDAA1C are in the prepubertal group (5–9 years) with better insulin sensitivity. The two definitions agree for 71.4% of the prepubertal and the older group of patients (average for 6- and 12-month values).

Stability of definitions

During the period 6–12 months after diagnosis, the change in frequency of partial remission as assessed by IDAA1C, A1C, insulin dose, and stimulated C-peptide is illustrated in Table 1. With IDAA1C ≤9, only 1 patient entered partial remission and 61 patients ended partial remission; with A1C ≤7.5%, 15 entered partial remission and 53 ended; with insulin dose ≤0.5 units · kg^{-1} · 24 h^{-1}, 5 entered partial remission and 66 ended; and with stimulated C-peptide (>300 pmol/l), 9 entered partial remission and 49 ended.

CONCLUSIONS

— We have suggested a novel definition: A1C (%) + [4 × insulin dose (units per kilogram per 24 h)] ≤9 for the partial remission period in children and adolescents with type 1 diabetes (Fig. 1*A*). This practical and simply calculated definition is useful as it relates insulin dose and measured A1C to the preservation of β-cell function (C-peptide levels). This measure, adjusting for exogenous insulin, can be used as a quantitative measure of the underlying and theoretically untreated disease, and in this setting, it is superior to a definition using A1C alone.

This definition also avoids the necessity of measurement of C-peptide levels, which is laborious, expensive, and often unavailable. Generally, there was good agreement between these two measures (IDAA1C and C-peptide) (Fig. 1*C*), although we saw a different pattern over age (Fig. 1*B* and *E*), as discussed below. With either A1C ≤7.5% or IDAA1C ≤9, the

maximum partial remission in all age-groups was reached at ~3 months after diagnosis (Fig. 1*B*), which is in accordance with other studies (11,18). In addition, the IDAA1C correctly identified those in partial remission from the very start, whereas a partial remission definition by insulin dosage ≤0.5 units · kg^{-1} · 24 h^{-1} misclassifies a proportion of patients early in the disease because of a lack of or delay in insulin treatment around the time of diagnosis (Fig. 1*C*). This misclassification may be of importance for selection of patients for intervention studies aimed to protect islet cell function. Because IDAA1C is based on a joint evaluation of C-peptide, A1C, and insulin dose, the agreement of those in partial remission by the C-peptide definition is better for IDAA1C than for A1C alone (Fig. 1*D*), which was also shown in the χ^2 test of the relationship between the two measures and stimulated C-peptide.

Interestingly, the residual β-cell function was highest in the age-group 10–15 years during the whole study period, and this finding is comparable to the observations of the U.S. multicenter national study group, Type 1 Diabetes TrialNet (13). However, the new definition indicates that the frequency of partial remission was not higher in this group of patients compared with the school-age children 5–10 years old. Likewise, the mean daily insulin dose was higher in the older age-group (10–15 years) than in the younger age-group (5–10 years), perhaps indicating higher insulin resistance during puberty (19). Thus, the degree of hyperglycemia is determined not only by the β-cell function or insulin resistance but also by results from a combination of these two factors, which is reflected in the new definition. Therefore, IDAA1C was in agreement with stimulated C-peptide in 71.4% of the prepubertal and older patients in partial remission (Fig. 1*E*).

It is important to know the relationship of IDAA1C and stimulated C-peptide during the 1st year in new-onset type 1 diabetes. Overall IDAA1C showed a good correlation with the residual β-cell function as assessed by stimulated C-peptide (R^2 = 31%). This agreement level compares well with the homeostasis model assessment (14) in which estimates of β-cell function correlated with those for the hyperglycemic clamp (37%) and the intravenous glucose tolerance test (41%). In addition, IDAA1C at 6 months was the best predictor of stimulated C-peptide concentrations at 6 and 12 months compared with A1C and insulin dose. This result shows that IDAA1C overall is a good estimate of stimulated C-peptide in type 1 diabetes.

In terms of stability over time, only one patient was found to enter partial remission between 6 and 12 months. When spontaneous partial remission occurs in prepubertal or pubertal patients, it occurs most often within the first 4 months and infrequently after 6 months (20,21). This is a strong endorsement of the new IDAA1C definition because all other definitions discussed have higher numbers of patients that seem to enter partial remission in the period from 6 to 12 months (Table 1).

The new formula is very easy and practical to use in the clinic where a diabetes nurse specialist takes care of many aspects of daily management during the first months after diagnosis. At each visit in the outpatient clinic, the IDAA1C can be calculated by the nurse to check that the patient is still in remission, particularly if he or she does not frequently measure blood glucose or record data. If this is not the case, the patient may need to be referred to a pediatric diabetologist for changes in insulin management. Already this measurement has improved the delivery of diabetes care in some of our clinics and has led to a smooth transition to more individual treatment regimens.

Direct measurement of C-peptide has been recommended to provide the most appropriate primary outcome in trials evaluating the efficacy of therapies to preserve β-cell function (13). The new IDAA1C should be beneficial for research in this area because it might remove the need for intrusive investigations. It takes into account the glycemic consequences of a change in residual β-cell function. C-peptide measurements alone do not provide this information. In addition, the model should make it easier to select children and adolescents with significant endogenous insulin production and evaluate clinically meaningful changes in intervention therapies (22) that are aimed to preserve/regenerate β-cell function in new-onset type 1 diabetes.

In summary, the new insulin dose–adjusted definition of the partial remission period gives the best agreement with the stimulated C-peptide definition, is convenient and easy to use, and is associated with a stimulated C-peptide response of >300 pmol/l.

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